Radiotherapy and Oncology 114 (2015) 276–281

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Spacers in prostate IMRT

Spacers in radiotherapy treatment of prostate cancer: Is reduction of toxicity cost-effective?

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ARTICLE INFO

Article history:
Received 18 April 2014
Received in revised form 5 January 2015
Accepted 6 January 2015
Available online 20 January 2015

Keywords:
Prostate cancer
Radiotherapy
Toxicity-reduction
Spacer
Cost-effectiveness

ABSTRACT

Background and purpose: To compare the cost-effectiveness of treating prostate cancer patients with intensity-modulated radiation therapy and a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O).

Materials and methods: A decision-analytic Markov model was constructed to examine the effect of late rectal toxicity and compare the costs and quality-adjusted Life Years (QALYs) of IMRT-O and IMRT+S. The main assumption of this modeling study was that disease progression, genito-urinary toxicity and survival were equal for both comparators.

Results: For all patients, IMRT+S revealed a lower toxicity than IMRT-O. Treatment follow-up and toxicity costs for IMRT-O and IMRT+S amounted to €1604 and €1444, respectively, thus saving €160 on the complication costs at an extra charge of €1700 for the spacer in IMRT+S. The QALYs yielded for IMRT-O and IMRT+S were 3.542 and 3.570, respectively. This results in an incremental cost-effectiveness ratio (ICER) of €55,880 per QALY gained. For a ceiling ratio of €80,000, IMRT+S had a 77% probability of being cost-effective.

Conclusion: IMRT+S is cost-effective compared to IMRT-O based on its potential to reduce radiotherapy-related toxicity.

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In the past decade, intensity-modulated radiation therapy (IMRT) has become a widely used treatment for localized prostate cancer. Although IMRT enables highly conformal dose distributions, there is still a potential risk of patients developing severe gastrointestinal (GI) toxicity [1]. Various devices have been developed to spare rectal structures [2]. These can be divided into endo-rectal balloons (ERBs) that increase the distance from the dorsal rectal wall to the prostate and relatively novel spacers that separate the anterior rectal wall from the prostate by injecting an absorbable hydrogel or saline-filled balloon that naturally biodegrades within 6 months after implantation (Fig. 1). Several studies have confirmed both a decrease in calculated rectal dose and a decrease in clinically observed rectal toxicity [3–8] when using a spacer.

Although pilot studies and clinical studies are available on the dosimetric and outcome effects of a spacer, no cost-effectiveness analyses have been conducted so far. Due to ever-expanding health care expenses, knowledge about the cost of treatments is continuously gaining importance. Particularly knowledge on how extra costs are related to the additional gain in health related outcome of treatments, which might be either a gain in overall survival, or a benefit in quality of life. This study aims to provide insight into the cost-effectiveness of a spacer, relating the extra costs to the gain in quality of life through reduction in rectal side effects in patients with prostate cancer.

The objective of this modeling study is to look at the cost-effectiveness of a toxicity-reducing spacer for prostate cancer patients by comparing IMRT therapy with a spacer (IMRT+S) versus IMRT-only without a spacer (IMRT-O). It gives an overview of the economic consequences before introducing this new approach into standard practice.

Materials and methods

Decision-model: Markov model

To assess whether the additional spacer costs are justified given the expected reduction in toxicity, a decision-analytic Markov model

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http://dx.doi.org/10.1016/j.radonc.2015.01.005
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was constructed to compare the expected costs and effects of IMRT-O with IMRT+S. Toxicity (i.e., grade ⩾2 late rectal bleeding) and associated costs were modeled over a 5 year time horizon, because the incidence of events occurring after 5 years is small. In this model, a hypothetical cohort of prostate cancer patients moves between mutually exclusive health states according to a set of transition probabilities. The cycle length of the model was set to one year.

Markov model input

The inputs for the Markov model are based on a published nomogram that relates dose–volume histogram to the risk of rectal bleeding [9] and studies published on complications-related costs and quality of life [10] (Table 1). Health states were based on whether patients were alive and had mild or no side-effects and whether they had grade ⩾2 late rectal bleeding (Fig. 2). Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 4.0 (CTCAE) [11]. The final absorbing state was 'death', either due to cancer or other causes. The Markov model was built and analyzed in Microsoft Office Excel 2007.

Transition probabilities

Transition probabilities were derived from the literature for each cycle; the input parameters are listed in Table 1. Considering that the percentage volume of rectum receiving >75 Gy (V_{75}^{rectum}) is one of the inputs in the nomogram for predicting radiation-induced toxicity in prostate cancer patients, we used the Valdagni nomogram to estimate the risk of late rectal bleeding [9]. The prediction model of Valdagni is based on patients enrolled in 2002–2004. The mean percentages of 5.5% and 1.2% for V_{75}^{rectum} after IMRT-O and IMRT+S were derived from the literature [12].

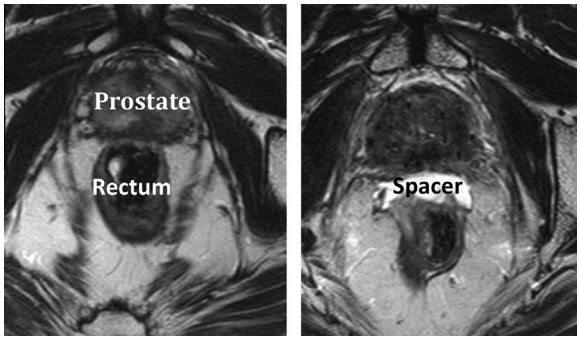

Fig. 1. Axial T2 magnetic resonance images of a patient with a spacer before injection (a) and after injection (b).

Effects and costs

Quality of life

The use of utility scores allows for the calculation of Quality Adjusted Life Years (QALYs) and cost per QALY ratios. The model uses health-related quality of life in terms of utility scores as an outcome measure. Utility scores provide a single index value for health status, ranging from 0 (representing death) to 1 (representing perfect health) [13]. Utility scores were derived from the literature and are listed in Table 1. The utility for prostate cancer patients was derived by using the EuroQol (EQ-5D) instrument before and 6 months after completion of radiation [14]. The future effects were discounted to their present value by a rate of 1.5%, according to Dutch guidelines [15].

Costs

As there is no standard treatment for late GI toxicity, the following assumptions were based on expert opinion. Grade 2 is mostly treated with low cost items such as diets or medication. Patients with grade 3 toxicity have on average 2 flexible sigmoidoscopies and blood transfusions. Some patients with more severe cases of GI toxicity may need more procedures such as laser treatment: it was assumed that patients with grade 3 toxicity would have on average 2 laser therapy sessions. The average monitoring and treatment costs for the treatment of all late GI toxic effects was calculated using the proportions of patients with grade 2 and 3 toxic effects. The proportion of grade 3 toxicity of all grade 2 and 3 effects was 25%. All costs were reported in euros (€) and are listed in detail in Table 2. Price indices were used to convert costs to the 2012 price level. Where possible, unit costs were based on the Dutch manual for cost research [16]. Since the costs of IMRT in both treatment strategies are similar, once-only treatment costs solely consisted of spacer costs (i.e., the application of the spacer plus the cost of the spacer itself). In addition, the calculation took into account the cost of standard follow-up and treatment-related complications over the modeled period (Supplementary Table 1). Future costs were discounted to their present value by a rate of 4% [15].

Markov model analysis

Over a 5 year time horizon, the expected mean costs, occurrence of toxicity, and QALYs were estimated for all comparators. Subsequently, the incremental cost-effectiveness ratio (ICER) was

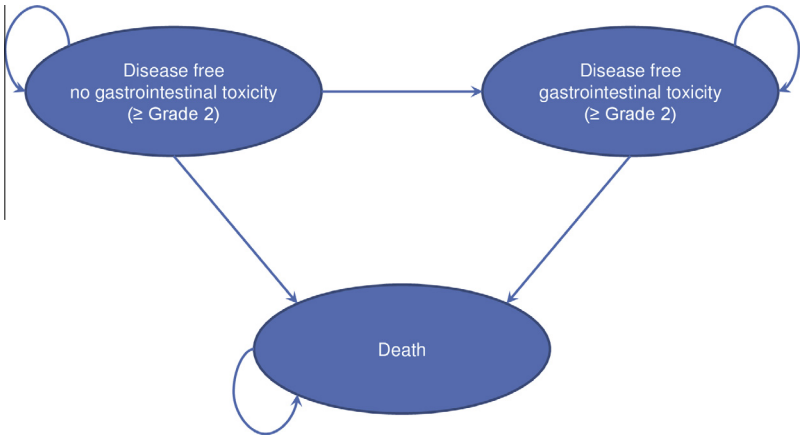

Fig. 2. Diagrammatic representation of the Markov model.

Table 1
Input parameters for base case Markov model.

	IMRT+S	IMRT-O	Source
Effectiveness			
Rectum V75%	1.2%	5.5%	[12]
Total probability at 5 years of GI grade 2 or higher	6%	10%	[9]
Utilities			
Prostate cancer without treatment-related toxicity	0.9		[14]
Prostate cancer with severe late GI toxicity (grade $\geqslant$2)	0.727		[10]
Costs (in euros)			
Cost follow-up prostate cancer without treatment-related toxicity	€323		See details in Supplementary Table 1 (2010)
Cost late grade 2 GI toxicity	€478		See details in Supplementary Table 1 (2010)
Cost late grade 3 GI toxicity	€4104		See details in Supplementary Table 1 (2010)
Proportion grade 2 (of all grade 2 and 3)	0.75		[19]
Spacer treatment (material and implantation)	€1700	–	See details in Table 2

Table 2
Cost-effectiveness analyses results.

	IMRT+S	IMRT-O	Incremental
Life years gained	4.189	4.189	0.000
(95% CI)	(4.187–4.191)	(4.187–4.191)	
QALY gained	3.570	3.542	0.028
(95% CI)	(3.126–3.855)	(3.119–3.817)	(0.006–0.05)
Spacer treatment costs*	€1700	€0	€1700
Radiotherapy follow-up and toxicity costs** (95% CI)	€1444	€1604	−€160
	(€1032–€1853)	(€1290–€1947)	
Total cost (95% CI)	€3144	€1604	€1540
			(€1239–€1838)
Incremental cost per QALY gained (95% CI)			€55,880
			(€27,796–€212,895)

Abbreviations: CI = confidence interval; LY = life year; QALY = quality-adjusted life year.
* Compromises the cost of the spacer itself: €1300. The rest is an estimation of the use of an ultrasound and template, the collaboration with an urologist, materials, care on department, eventually extra imaging. Minimum €1300, maximum €2100.
** Comprises the cost components: follow-up (€323 annually), late grade 2 GI toxicity (€478 annually) and late grade 3 GI toxicity (€4104 annually) assuming a proportion grade 2 (of all grade 2 and 3) of 0.75.

calculated by dividing the incremental costs by the incremental QALYs. The ICER represents the costs of an additional QALY gained when comparing two strategies. Whether a treatment strategy is considered cost-effective depends on how much society is willing to pay per gained QALY, which is referred to as the ceiling ratio. We adopted a ceiling ratio of €80,000, which is the informal ceiling ratio for a high burden of disease in the Netherlands [17].

To illustrate the results of the simulation, a cost-effectiveness acceptability curve (CEAC) was calculated [18]. A CEAC shows the probability that a treatment has the highest net monetary benefit, and thus is cost-effective, given different ceiling ratios. It simultaneously shows the probability that the 'wrong' decision will be made by implementing the treatment that, based on the currently available evidence, appears to be the most cost-effective.

Markov model assumptions

The main assumption was that the disease progression and survival rates were equal for the two treatments. A conservative assumption was made that the utility decrement related to severe late GI toxicity (grade $\geqslant$2) was independent on other toxicities (genito-urinary (GU) toxicity (all grades), GI grade 1 toxicity and erectile dysfunction) and progression. No PSA survival difference was assumed because it was considered that in both arms the received radiotherapy dose was similar and equivalent to 78 Gy. The late GI toxicity was modeled as irreversible, which implied that some form of post-treatment intervention is necessary. Since the occurrence of complications due to the spacer is expected to be very low and data were lacking on this parameter, complications were ignored in the base case (the reference case).

IMRT techniques for both treatment strategies were assumed to be 'equal' in terms of costs, that is, to have the same fractionation schedule, dose delivery and treatment planning technique. Finally, we assumed that 75% of the total rectal toxicity (grade 2 and 3) would be grade 2 [19].

Sensitivity analyses

Sensitivity analyses were performed to handle the uncertainty around the economic analysis [20]. One-way sensitivity analyses were conducted to determine the parameters to which the ICER is most sensitive. One-way sensitivity analyses were performed by varying selected model parameters based on the 95% confidence interval (CI) of the base-case estimate, where available, while keeping all other parameters constant. Results are shown in tornado diagrams, illustrating the impact of the range of each variable on the model's outcome. The variables are ordered with those with the broadest range of impact on the top. Variables with progressively narrower ranges of impact are placed below, giving an appearance similar to that of a tornado. CIs were not available for the costs used in the model. Hence, all other costs were modeled using the minimum and maximum values specified in Supplementary Table 1.

Results

Cost-effectiveness of IMRT+S versus IMRT-O

The combined follow-up and toxicity costs were estimated at €1444 and €1604 for IMRT+S and IMRT-O, respectively, thus saving

€160 on the complication costs in favor of IMRT+S. Adding the spacer costs of €1700 resulted in a total cost of €3144 for IMRT+S.

The QALYs yielded were 3.542 and 3.570 for IMRT-O and IMRT+S, respectively. IMRT+S thus produces 0.028 QALYs more than IMRT-O. When all costs and effects are discounted by 4% and 1.5% respectively, IMRT+S costs an additional €1540 per patient. Hence, IMRT+S is more expensive than IMRT-O, but the former produces 0.028 additional QALYs.

This results in an ICER of €55,880 per QALY gained. For the ceiling ratio of €80,000, IMRT+S had a high probability of being cost-effective (77%). The cost-effectiveness acceptability curve is presented in Fig. 3.

Sensitivity analyses

The one-way sensitivity analyses are presented using a Tornado diagram (Fig. 4). The results revealed that IMRT+S remained cost-effective in most scenarios, given a ceiling ratio of €80,000 is adopted. Further analyses found IMRT+S to be cost-effective if the utility of healthy patients was more than 0.845 and if the GI toxicity utility was less than 0.78. The model was most sensitive to variations in the healthy utility, with no GI toxicity; the net benefit varied from €35.414 to €127.963. The model was the least sensitive to variations in overall survival, in which the net benefit ranged from €55.444 to €55.507. The model stayed cost-effective to variations of cost of spacer and implementation procedure (range from €1300 to €2100).

Discussion

To our knowledge, this is the first study to examine the cost-effectiveness of spacers for a GI toxicity-reducing strategy in IMRT therapy for prostate cancer.

The external beam RT for localized prostate cancer has evolved as a result of the introduction of IMRT. Still, GI toxicity does occur and its resulting reduction of quality of life cannot be ignored. Dose-escalated IMRT beyond 78 Gy prescription dose has raised the rates of acute and chronic grade $\geqslant 2$ rectal toxicity from 3% to 20% and 5% to 21%, respectively [21–23]. The risk of rectal toxicity depends on the volume of the rectum that receives a high radiation dose [24]. In a large prospective series, the percentage volume of rectum receiving >70 Gy (V_{70}^{rectum}) correlated with the occurrence of chronic rectal toxicity. Grade $\geqslant 2$ chronic rectal toxicity occurred in 54% and 13% of patients in whom the V_{70}^{rectum} was >26.2% and $\leqslant$26.2%, respectively [25]. It is therefore important to implement techniques that prevent these high rectal volume doses. As the prostate is directly adjacent to the rectal wall, the anterior rectal wall cannot be spared completely from the high dose region irrespective of the radiation technique.

In the past decade several research groups have investigated physically separating the rectum from the prostate (e.g., by injecting a hydrogel) to reduce the rectal dose and improve quality of life after treatment. Tests have previously been carried out in which the space between the prostate and rectum was injected with hyaluronic acid, human collagen or PEG-based hydrogel [3–8]. All studies confirmed a decrease of the rectal dose when using an absorbable spacer: Prada et al. and Wilder et al. [3,4] reported no rectal bleeding with the use of spacers versus no spacers. Noyes et al. and Uhl et al. [5,6] showed a 50% and 60.3% dose reduction of the rectal wall, respectively. Pinkawa et al. [7] found a 59% decrease in rectal V_{70}. A multi institutional trial resulted in $\geqslant$7.5-mm prostate-rectal separation in 95.8% of patients; 95.7% had decreased rectal V_{70} of $\geqslant$25%, with a mean reduction of 8.0 Gy [12].

No side effects were described due to the application. Results from a simulation study with IMRT planning of cadaveric specimens showed that a prostate-rectum separation of 10 mm was sufficient to reduce the mean rectal V70 by 83.1% ($p < 0.05$) [26]. These results confirm a decrease of rectal dose when using an absorbable spacer and a decrease of rectal toxicity. The results presented in this paper are valuable for decision-making in terms of policy making and future research. If all the assumptions are correct, IMRT+S is less toxic and more effective than IMRT-O for all prostate cancer patients. Sensitivity analysis revealed that the model was robust to changes in individual parameters and IMRT+S remained cost-effective in most scenarios given a ceiling ratio of €80,000 is adopted.

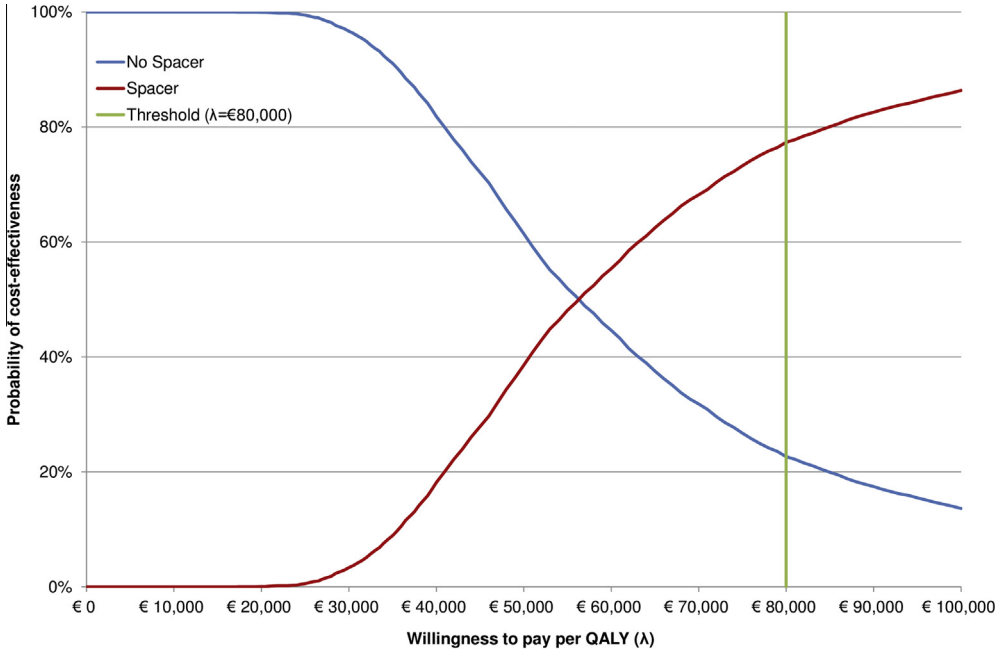

Fig. 3. Cost-effectiveness acceptability curve (CEAC) for IMRT with and without a spacer, showing that the probability of a spacer being cost-effective based on a willingness to pay of €80,000 per QALY is 77%. The vertical line represents the ceiling ratio that was adopted in our analyses (€80,000/QALY).

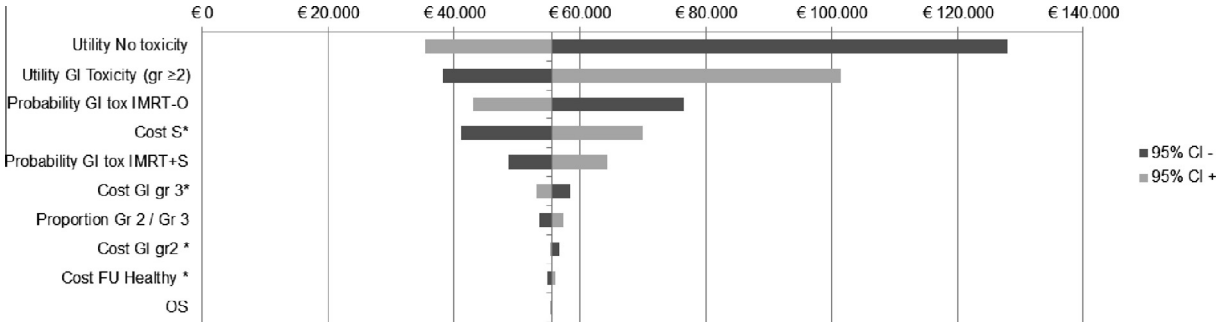

Fig. 4. A Tornado diagram showing the sensitivity analysis, using the 95% CI of all the input factors of the model. Each bar depicts the overall effect on net benefits as that input is varied across the indicated range of values, while other input variables are held constant. The vertical line indicates the base case. *Range is used instead of 95%CI.

The main research implication is that the applied study method is a feasible and informative method to explore the potential cost-effectiveness of the spacer in individual patients and different RT techniques, such as stereotactic body RT (SBRT).

If we acknowledge patient heterogeneity and we can select a population of patients with a high risk of late rectal complications (e.g., re-irradiation, inflammatory bowel disease, diabetes mellitus [27] or anticoagulantia [28]), the cost-effectiveness of the spacer will most likely improve because those patients will benefit even more from the use of a spacer.

This study has several limitations, inherent to its design, worth mentioning. As all early economic studies of new techniques, including this one, it is limited by clinical data comparing those two treatment modes. The procedures for placing the spacer could have some disadvantages. Potential side effects could occur such as pain, rectal perforation and abscess, although not reported so far. These risk factors are not yet fully described and are estimated to be very low (<5%) [4]. The costs incurred with these risk factors have not been included. As discussed by Vordermark et al. [29], the side effects of the injection must be followed prospectively.

A longer follow-up is needed to obtain a larger patient cohort to assess how a rectal dose reduction will impact on late rectal toxicity in patients undergoing spacer insertion. Next, it is important to note that the available prediction model developed by Valdagni et al. [9] was used to predict the occurrence of toxicity. As with all prediction models, these models can possibly be optimized to achieve more accurate predictions. The prediction model of Valdagni is based on patients enrolled in 2002–2004, using an older technique. Newer radiation techniques, as image-guided radiation therapy or volumetric arc therapy, enable dose painting around the prostate with a consequent enhancement of non-dosimetric predictors of rectal toxicity.

The ceiling of €80,000 per QALY is a basis for debate: willingness-to-pay values per QALY gained differ across countries. In the UK £20,000–£30,000 per QALY has been accepted as the threshold to decide whether or not the National Institute for Health and Clinical Excellence (NICE) should recommend use of a new healthcare technology [30].

In the US, the threshold of $50,000–$100,000 per QALY often is mentioned in medical literature. The Australian Pharmaceutical Benefits Advisory Committee was unlikely to recommend a drug or treatment for listing if the ICER exceeded AU $76,000. This uncertainty of threshold levels has an impact on the implications of cost-effectiveness results.

Finally, GU toxicity and erectile dysfunction were not modeled. Weber et al. [31] have shown that administrating a spacer may increase the delivered dose to the bladder by displacing the prostate gland anteriorly. However this increase in dose–volume metrics is non-significant in a majority of cases. Also, given the lack of dose–volume data, it is doubtful that the modified dosimetry after spacer injection could lead to an increase in GU toxicity. This is confirmed by Song et al. [12], who showed that the V70 of the bladder is lower with the use of a spacer than without.

In conclusion, the current paper demonstrates that, according to the Dutch health costs and based on the applied assumptions are correct, the spacer can be cost-effective for prostate cancer patients due to less severe toxicity and a reduction in treatment costs associated with these side effects. The incremental cost-effectiveness ratio of IMRT+S versus IMRT-O was €55.880 per QALY gained. IMRT+S has a 77% probability of being cost effective at a willingness-to-pay value of €80,000 per QALY gained. The cost-effectiveness of the spacer is expected to increase if patient heterogeneity is acknowledged.

Conflict of interest

No disclosure.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.01.005.

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